

Imaging in radiotherapy

Report of the Consultant's Meeting

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FOREWORD

The adaptation and integration of imaging into the process of cancer detection, diagnosis, and intervention is an area of medicine that is undergoing extremely rapid development. Radiation therapy is a prime example of this change. The role of the medical physicist in the radiation therapy process accelerates the development and introduction of these technologies into the clinical setting. As a result, imaging is now a pervasive component of radiation therapy with all major imaging modalities represented and numerous examples in which these modalities have been used in treatment planning to allow increased accuracy and precision in the delivery of dose. While the objectives of these developments are clear, they raise numerous issues regarding the skills and resources that assure these technologies are appropriately integrated and applied. Specifically, these developments place enormous pressure on the clinical staff to extend their knowledge base and their scope of responsibility.

The IAEA assembled a team of medical physicists with experience in radiation therapy and imaging consisting of: D. Jaffray (Princess Margaret Hospital, Toronto, Canada), P. Keall (Stanford University Cancer Center, Stanford, USA), B. Mijnheer (The Netherlands Cancer Institute, Amsterdam, The Netherlands), M.O. Leach (The Institute of Cancer Research and The Royal Marsden Hospital, Sutton, United Kingdom), J. Humm (Memorial Sloan-Kettering Cancer Center, New York, USA) and charged them to examine the increasing role of imaging in the radiation therapy process and make recommendations related to their observations. The current report provides a perspective on the issues related to imaging in radiation therapy assisting the Agency in accommodating these issues in the years ahead.

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CHAPTER 1. OVERVIEW, OBJECTIVES, AND CHARGE OF CONSULTANTS

The high rate of technology advancement in today's world is astounding. These technological advances are having an enormous impact on all aspects of life and their impact on the practice of medicine is not to be underestimated. One area of medicine that is undergoing extremely rapid development is the adaptation and integration of imaging into the process of cancer detection, diagnosis, and intervention. Radiation therapy is a prime example of this change. The role of the medical physicist in the radiation therapy process accelerates the development and introduction of these technologies into the clinical setting. As a result, imaging is now a pervasive component of radiation therapy with all major imaging modalities represented and numerous examples in which these modalities have been adapted to the treatment machine to allow increased accuracy and precision in the delivery of dose. While the objectives of these developments are clear, they raise numerous issues regarding the skills and resources that ensure these technologies are appropriately integrated and applied. Specifically, these developments place enormous pressure on the clinical staff to extend their knowledge base and their scope of responsibility.

In 2007, the IAEA assembled a team of medical physicists with experience in radiation therapy and imaging and charged them to examine the increasing role of imaging in the radiation therapy process and make recommendations related to their observations. A report was commissioned that should achieve the following objectives.

- *Review the status of mature imaging modalities currently employed in radiation therapy practice. These include pre-treatment imaging for target definition to in-room imaging for improved precision and accuracy of delivery.*
- *Review the availability and applicability of existing practice and quality assurance guidance documents related to the use of imaging information in the radiation therapy process.*
- *Identify of shortcomings in these documents while being cognizant of the broad range of needs found in the IAEA Member states.*
- *Develop a set of recommendations to the IAEA related to the needs and opportunities for further development with respect to imaging in radiation therapy. These recommendations may take the form of either detailed, prescriptive recommendations (e.g. formation of a CRP, preparation of a TECDOC) or broader recommendations regarding future directions.*

The resulting report was to be employed for internal use by the Agency, providing a perspective on the issues related to imaging in radiation therapy and assisting the Agency in accommodating these issues in the years ahead.

CHAPTER 2. IMAGING IN THE RADIOTHERAPY PROCESS

In the developed countries, radiation therapy is employed in over 50% of cancer patients at some point in the management of their disease. As a local therapy, radiation therapy seeks to exploit technology to conform the treatment to the targeted structure while avoiding surrounding critical normal tissue. Overall, the process of radiation therapy has become increasingly complex as the technology for its delivery advances. Recent developments in radiation collimation (e.g. multi-leaf collimators), computation (inverse planning), and imaging (target definition and targeting) have resulted in a far more complex radiation therapy process which promises higher quality of intervention, dose escalation, and/or reduced toxicity. The radiation therapy process contains many steps with imaging distributed throughout the process.

Imaging has become the primary source of information in the design of radiation therapy. As such, it is of critical importance that (i) the signal contained in these images is well understood, and, (ii) the spatial distribution is precise and accurate. Failure in this aspect to do so can result in serious deleterious effects including failure to control the disease and/or induction of unforeseen toxicities.

2.1. Imaging for target determination

The use of imaging to define the cancer target is, in many ways, ideal, however, it is important to understand the limits of the imaging signal if it is to be appropriately applied. As with any measurement, it is useful to consider the precision and accuracy of the reported signal. The precision relates to the minimum quantity that can be detected by the system and the accuracy of its spatial resolution. In the context of cancer, this is highly relevant when considering the desire to treat not only the gross tumor volume (GTV) but also deliver a dose to the surrounding clinical target volume (CTV), which may contain microscopic extension of the disease and is by definition not visible on the available images. Incorrect interpretation of the imaging signal can result in either underestimating or overestimating the extent of these volumes. It can be anticipated that this problem will persist regardless of the specific imaging modality being employed. The complex nature of the disease makes complete characterization of the radiation target via imaging somewhat unlikely. As a result, the imaging systems effectively provide surrogate signals of the disease (e.g., a mass on a CT image). These surrogates are often referred to as ‘the target’ although they are clearly not a precise or accurate representation. It is important to emphasize that the image signal is, therefore, only a surrogate of the target and must not be over-interpreted. In fact, the traditional practice of treating to bony anatomy recognizes that the bones are reasonable surrogates of the adjacent disease targets.

As in any measurement, there can be uncertainty in the quantities extracted from images. This is particularly the case in the determination of target location in treatment planning images (e.g., CT images for planning). Given that there are random uncertainties in any measurement, it is reasonable to expect that any image that is used to design the therapy will contain some geometric deviation from the mean. As a result, the use of such an image to design the therapy can introduce a systematic error that will persist over the course of therapy. The sources of this deviation are numerous and include, for example, momentary displacement of an internal structure at the time of planning image acquisition (e.g., rectal gas) or the random variations in the contouring of the structure by a busy clinician. In addition, there could also be systematic errors associated with a miscalibration of scale in an imaging system or sag in the level of the imaging couch.

As the field seeks dose escalation and reduced normal tissue complications, the need to reduce, manage and accommodate these uncertainties has been highlighted. The development of ICRU guidance documents on radiation prescription [1, 2] has created an important vehicle for development of image-based radiation therapy. The concept of the planning target volume (PTV) has allowed the radiation therapy field to relate the geometric uncertainties to a volume that can be included in the design of an appropriate dose distribution.

2.2. Imaging Modalities in Use in Radiation Therapy

2.2.1. Computed Tomography

2.2.1.1. Current Issues and Future Developments

Computed tomography (CT) is and will be likely to remain the predominant volumetric imaging modality for radiotherapy. In common with other volumetric imaging modalities, CT is used to delineate tumour (Gross Tumour Volume, GTV), suspected tumour (Clinical Target Volume, CTV) and normal structures. Margins are assigned for geometric uncertainties, creating the Planning Target Volume (PTV) and Planning Organ-At-Risk Volumes (PRV).

In addition to its role in structure delineation, CT is the primary modality for treatment simulation and treatment planning, including dose calculation. The role of CT in simulation requires that geometric fidelity of the image faithfully representing the object, both at the CT scanner and after transfer to the treatment planning system (TPS) is critical. The role of CT in dose calculation means that an appropriate CT number-to-electron-density conversion is developed and tested in the TPS, both for validation of the density of the object being scanned, as well as for the effect of heterogeneities on the dose calculation algorithm. The CT scan also forms the basis for the digitally reconstructed radiograph (DRR), which is used as the template for verifying delivery using portal imaging or in-room or gantry mounted kV imaging. Note that there are efforts to perform the entire CT simulation-planning-treatment process efficiently in a single session on a linear accelerator with volumetric imaging linked to a treatment planning system [3].

There are two main methods of CT simulation. The first involves the alignment of the patient, often with the aid of a CT scout view to ensure appropriate skeletal alignment, with the marking of the patient isocenter with a tattoo and overlaid radioopaque marker prior to the scan. The second approach to CT simulation involves the assignment of the isocenter after the patient scan, the identification of which occurs through the shifting of the couch and external lasers. The isocenter is typically marked with tattoos at the intersection of the lasers. The second approach has the advantage that the CT itself can be used for the isocenter selection, but this is perhaps outweighed by the disadvantage that patient motion between the imaging and the final marking, and miscalibrated external lasers and couch sag can cause systematic errors to be introduced to the radiotherapy process. For both approaches, careful attention to appropriate patient immobilization and recording the patient pose for reproduction of the set-up during treatment delivery are critical to accurate radiotherapy.

In order to accommodate patient position and immobilization devices for radiotherapy treatments, large bore (>70 cm) CT scanners are popular for CT simulation. Large bore dedicated PET-CT simulators are also available.

2.2.1.2. Issues

CT in radiotherapy is a well established and mature technology and enables 3-D conformal and intensity modulated radiotherapy. Nevertheless, for institutions that do not have 3-D technology, the 2-D to 3-D transition is a significant change. Training is needed on 3-D imaging, planning, data transfer, process QA and delivery. An IAEA TECDOC under development entitled *Transition from 2-D to 3-D Conformal and Intensity Modulated Radiotherapy* is addressing this issue.

A QA programme for the CT simulation process should address the following points: radiation safety, dosimetry, laser/couch and other geometric alignment, image quality including geometry and HU-density at CT and TPS, and DRR production.

2.2.1.3. Review of Guidance Documents

Comprehensive guidelines for the quality assurance for CT simulators and the CT-simulation process are given in the report of the AAPM Task Group TG 66 [4]¹. This document is comprehensive and discusses appropriate quality assurance tests to be performed for image acquisition, image transfer, treatment planning and DRR generation. An important extension of the TG 66 report is the addition of dose validation in the 'Sample overall CT-simulator process test'. The addition of dose validation to these end-to-end, or integral process tests is a recommendation of this consultant group.

Further guidelines for CT simulator QA can be found in the IAEA textbook [5]² (particularly chapter 12), and also IPEM report 81 [6]. Several websites have useful information on CT and CT simulation^{3,4,5}.

There is a general lack of education on CT simulation and imaging requirements for radiotherapy. This could be partly assisted by supplementing the continuing IAEA efforts in the *Clinical training guide for radiation oncology* initiative. No freely available web-based training on CT simulators exists. The IAEA is recommended to assist in filling the void in education. There is an opportunity to collaborate with the ongoing efforts of AAPM TG #131: Medical Physics Training in Developing Countries.

There is an increased focus on the management of respiratory motion in radiotherapy [7]⁶. One approach to manage respiratory motion is to acquire respiratory correlated, or 4-D, thoracic CT scans. 4D-CT can be used for estimated tumour and normal tissue motion and can form the basis of motion-inclusive, respiratory-gated or tumour-tracking planning and delivery. 4D CT results in an order of magnitude more imaging data to be acquired, processed, stored and used for planning [8]. This technology is maturing, and further guidelines for the acquisition and specific applications of 4D-CT in radiotherapy are needed. Note that breath hold and abdominal compression approaches can also be used in the CT simulation process to manage respiratory motion.

¹ http://aapm.org/pubs/reports/rpt_83.pdf

² http://www-pub.iaea.org/MTCD/publications/PDF/Pub1196_web.pdf

³ <http://dosimetrytrainingtool.com/dtt/portal/portal>

⁴ <http://www.emerald2.eu/>

⁵ <http://impactsan.org/>

⁶ http://aapm.org/pubs/reports/RPT_91.pdf

CT can also be used for adaptive radiotherapy, in which the changing anatomy throughout the treatment course can partially be accounted for by an additional loop or loops through the CT-based process, using prior information of the anatomy, treatment plan and treatment delivery. Adaptive radiotherapy is clearly a treatment paradigm that will have a large impact on radiotherapy and the radiotherapy process, although as yet, there is little clinical implementation and few commercially available tools or guidance documents for adaptive radiotherapy.

2.2.2. Magnetic Resonance Imaging

2.2.2.1. Current use and future developments

Since its initial clinical use in the early 1980s, MR has become a core modality in most diagnostic oncology facilities, and the primary diagnostic resource for CNS disease. Based primarily on superconducting horizontal cylindrical 1.5T magnets, with a growing number of 3T cylindrical magnets and of lower field open magnets with vertical fields, MR utilises the changing mobility of water molecules to obtain a wide range of manipulable image contrasts, complemented by an increasing range of contrast agents. Spatial resolution is traded for signal to noise and imaging time and typically ranges from 0.5-2.0 mm, with a slice thickness typically ranging from 0.5-7.0 mm. Images are usually obtained as 2-D sets of slices or as 3-D volume acquisitions, and although usually obtained parallel or transaxial to the magnet axis they can generally be obtained at any arbitrary plane. Imaging currently uses multi component local coils to maximise signal. Each imaging acquisition involves specifying many adjustable parameters that can vary the appearance and properties of the image.

Recently, a range of functional imaging techniques has been introduced, using intrinsic contrast mechanisms such as blood oxygen level dependent (BOLD) approaches for brain activation, or water diffusion to provide maps of the apparent diffusion coefficient. Extrinsic contrast agents can inform on tumour properties, and modelling techniques can derive a range of functional parameters [9, 10]. Cellular metabolism can be monitored using MR spectroscopy, where either single voxels, or 2-D or 3-D metabolic maps are obtained [11].

There is increasing dependence of advanced radiotherapy techniques on image guidance [8]. MR often plays an important role in defining the location and local extent of disease. It provides a primary role in CNS disease, and in some diseases (e.g., prostate cancer [12]), head and neck cancer [13]). It defines organ or disease extent more accurately than other modalities. Bone marrow metastatic involvement and cord compression are seen well. Recent advances in ultra small super-paramagnetic iron oxide (USPIO) contrast agents offer the potential to identify lymph nodes with macroscopic involvement. Diffusion provides a sensitive method of identifying disease and following changes in cellularity, and it is showing promise in whole body surveys of metastatic disease and identifying involved lymph nodes, with potential to identify areas for treatment. Contrast agents often identify disease extent more clearly, depending on permeability of vasculature. Quantitative assessment allows functional tumour parameters to be calculated using models [9]. These techniques, together with spectroscopic mapping, may aid in defining tumour extent [14]. Cine-mode acquisitions can define target tissue motion [15]. Brain activation [16, 17] and tractography [18-20] may aid definition of CNS treatment volumes, and sparing of critical functions. Contrast agents and BOLD techniques may inform on tissue oxygenation [21] and MR based hypoxic markers are also being evaluated [22]. Polymer gels, read out by MRI, provide a powerful tool for mapping complex 3-D dose distributions [23, 24]. MR simulation has been developed at a number of centres [25, 26].

2.2.2.2. *Issues*

Generation of MR images is a complex process with many variables that may be affected by the user, during service, and with instrumental variability and drift. The geometric integrity of images is not dictated only by engineered components, but also by electronic controls. Practical considerations lead to intrinsically non-linear spatial relationships, particularly towards the edges of the field of view. Correction software may be provided, may be user accessible and switchable, and is unlikely to be completely accurate, to correct for drift in machine adjustment. It will also not correct for intrinsic distortions due to patient susceptibilities. Accurate correction methods for all of these have been proposed, but they rely on implementation of special sequences and the use of specific phantoms. Chemical shift artefact, due to a spatial shift in images from water-based tissues and from fat, can cause a problem particularly at the edge of the body and at tissue interfaces. This can be corrected by using a large imaging bandwidth or by the correction method identified above. Bone as well as air spaces, and with some sequences vascular spaces, produce a void in the MR image.

Imaging in the treatment position is recommended to reduce the demands on any subsequent registration. For this a flat table insert is required. Radiotherapy set-up lasers are required to minimise mis-registration and ensure longitudinal alignment. These are best incorporated when the facility is planned. Frames, masks and other equipment must be MR compatible and safe, and may require compromises with standard optimised imaging procedures, particularly in selection and location of radio frequency (RF) coils. Patients must be screened to ensure they have no contraindications to MR. Implants that are safe to scan may still produce large image artefacts. Motion may affect images in various ways, and produce a range of artefacts. Care needs to be taken in selecting image acquisition protocols that will provide positional information relevant to the planning process

Image acquisition methods can vary widely, and selection of parameters can vary the true spatial resolution of the sequence, which may not equate to pixel size. There are many potential artefacts that depend strongly on choice of image parameters. In spectroscopic imaging, selected voxel size may vary from 5-20 mm for ^1H , with the actual resolution being a complex function of location and imaging specification. Equally slice profile and effective slice width can also vary strongly both with imaging parameters and with the relaxation properties of the tissues. Image intensity values may vary across images, dependent on the site imaged, and a range of set up and instrumental parameters.

MR images provide information that is either visually transferred to CT, or outlines are generated that are transferred via registration and fusion directly to CT. Alternatively there is increasing interest in the direct use of MRI data for treatment planning, via bulk tissue attenuation coefficient assignment [27]. As well as assuring the accuracy of spatial information and its registration, it is also important to ensure that spatial orientation and displacement as well as signal intensity are correctly encoded in the DICOM headers and transferred successfully to the treatment planning system. MR can provide a number of data sets with differing imaging information, comprising a substantial volume of data. Protocols for appropriate selection and combination of data for target and critical normal tissue definition need to be established.

2.2.2.3. *Guidance Documents*

There are a number of guidance documents and papers relating to quality assurance and phantoms for MR, although most of these are not designed specifically for radiotherapy.

IPEM report 81 [6] is probably the most specific and does consider the QA required for the use of MRI images in radiotherapy. This introduces a range of standard MR QA tests, but as stated in the text, it draws attention to the problems rather than providing definitive advice. Some attention is given to the issue of spatial linearity, and existing test objects for spatial linearity, slice warp, resolution, relaxation parameters and signal to noise are considered. This may provide some of the parameters required where MR data are transferred to and registered with CT, and CT is used as the base image set for planning treatment. If MR is to be used directly, or where registration issues are to be minimised, more detailed QA is required. Reference to the section on CT provides a range of parameters that need to be defined and tested, including couch deflection and positioning accuracy, on board marker accuracy and external positioning laser accuracy. Tests for separation of points need to be extended to identify and correct image linearity in 3-D over the maximum field of view (head or body depending on use) and assure the accuracy of image orientation in left-right, anterior-posterior and head-foot directions. Signal-to-noise and contrast performance need to be assured both for head and body imaging. The utility and robustness of functional images, taking account of specific issues such as motion and coils, relating to individual organs or regions of the body, need to be addressed. Standardised acquisition and analysis protocols are desirable.

Documents specifically on MRI quality assurance include IPEM Report 80 [28], AAPM Report 28 [29], AAPM TG 1 [30], AAPM TG 6 [31], Lerski et al. [32], MDD [33], Purdy [34], Sano [35], Barker and Tofts [36], Firbank et al. [37], Chen et al. [38]. AAPM TG 117 is developing a report on the use of MR imaging in RT and stereotactic procedures. AAPM TG 132 is developing a report on image registration and data fusion in relation to radiotherapy. Walker et al. [39] described phantoms to accurately measure MR relaxation times.

Khoo et al. [40] reviewed the use of MRI in RT treatment planning. Mah [26] reports on the use of and QA of a low field MRI system used for radiotherapy simulation. Moore et al. [41] reports on the QA of CT and MRI images used for treatment planning and Koch et al. [42] have assessed the accuracy of MRI in planning lung cancer treatment. References [43-49] report on the accuracy of high precision radiotherapy techniques.

Finnigan et al. [50] reports on a spatial linearity phantom used to characterise MRI image distortion, and methods to correct this, with more recent work providing read out methods and more accurate correction methods for MR system distortions [51-54]. Mutic et al. [55] reports on multimodality registration for conformal radiotherapy. De Brabandere et al. [56] assessed the use of MRI and CT in assessing seed positioning in the prostate.

A series of papers describe phantoms and methods of signal analysis for magnetic resonance spectroscopy developed through an EU concerted action [57-59]. Although not developed with radiotherapy applications in mind, the methods proposed have usefulness in this area.

2.2.2.4. Summary

MR simulation and MR measurements are playing a growing role in planning radiotherapy treatments. A specification for minimum performance and quality assurance of MR devices and MR data used for MR simulation needs to be developed. This should include:

- Performance requirement for MR simulation including couch performance, patient alignment, spatial linearity, signal and contrast to noise, relaxation time linearity, sequences and approaches to enable delivery of accurate morphological and functional imaging

- Quality assurance requirements for MR data used for treatment simulation and planning, to ensure consistent and reliable data are provided for treatment planning.
- Suitable audit processes within radiotherapy and related imaging departments are required to provide assurance that MR images meet the required standards.

2.2.3. Positron Emission Tomography

2.2.3.1. Current Use and Future Developments

Nuclear imaging is a powerful tool that uses radiotracer principles to detect disease based on functional or metabolic irregularities of the disease process. Two detection modalities dominate this imaging domain: single photon emission computed tomography (SPECT) and positron emission tomography (PET). Where SPECT gamma camera imaging is routinely employed for diagnostic studies, at this point, its use for RT treatment planning is limited by inadequate spatial resolution (around 12-15 mm) since it has been explored by very few centres. As a consequence, the committee decided that this technology is not yet a mature component of the RT process and therefore it is not discussed further in this report. However, there are a number of commonalities between SPECT and PET and therefore issues and concerns discussed under PET apply to SPECT and SPECT-CT systems.

PET is playing an increasing role in the radiation therapy treatment planning process since the emergence in 2000 of combination PET-CT scanners followed by dedicated PET-CT simulators. Ninety-nine percent of all PET studies performed worldwide today use [¹⁸F] fluorodeoxyglucose (FDG), because of its known uptake in viable cancer cells and its availability without on-site cyclotron. As a consequence, current applications of PET for radiation oncology applications (in particular in the non-developed countries) focus on FDG.

The current use of PET-CT for radiotherapy includes 3 focus areas. The first is the use of FDG to better select patients undergoing radical radiotherapy by up or down-staging disease as well as to assist in the determination of the GTV, including differentiation of viable from necrotic tissue.

The second is the use of PET with novel tracers to ascertain specific tumour biologic and microenvironmental features relevant to the radiobiology of the cancer. PET is capable of imaging a wide variety of biochemical and biologic features of the tumour which are of potential radiobiological importance and could be utilized for patient management and treatment planning. By using such tracers (e.g., of hypoxia, angiogenesis, proliferation) PET can provide prognostic information on the aggressiveness of the cancer as well as information for a “dose painting” treatment [60, 61]. Such PET application, however, is not yet in routine clinical practice.

The third is the use of PET for the evaluation of tumour response based on imaging signals associated with tumour/tissue viability and metabolic changes, rather than anatomic changes acquired from the CT component of the PET-CT exam. Prospective monitoring of tumour response during a course of radiation therapy (at least with FDG) is probably neither practical nor useful given the confounds of radiation induced tumour cell death and inflammatory response. However, FDG PET scans performed at a consistent interval post-treatment may yield a reproducible measure of tumour response [62]. Evidence is available in studies of combined chemoradiation in esophageal cancers, colorectal cancers, lymphoma, etc. of the value of FDG in assessing the persistence or recurrence of viable tumour post therapy [63]. In

particular for reliable treatment response assessment, there are significant challenges to maintaining the constancy of PET camera performance over time.

2.2.3.2. Issues

It is common practice for radiation oncologists to use subjective judgment when defining target volumes from PET-CT image data. This can be problematic when arbitrary PET window display settings are used. Algorithms have been proposed that identify tumour boundaries on FDG PET images [62, 64, 65]. Numerous PET edge detection algorithms are under development, but much work is still required before reliable tumour segmentation algorithms can be used confidently for treatment planning. There is an issue of physician subjectivity versus objective algorithms of uncertain accuracy. Gold standard measures to aid the definition of objective criteria are sorely needed such as histological verification from patients undergoing surgery post FDG PET [66] and also from computer lesion simulations, where ground truth can verify the accuracy of different algorithms. Furthermore, for tumours located close to the diaphragm, the accuracy in defining tumour boundaries is limited also by the effects of respiratory movement, causing a loss in resolution, distortion and mis-registration between PET and the corresponding CT.

Defined quality assurance and protocol design procedures will be required to maintain consistency between studies at the same centre or in multi-centre trials. This is necessary to obtain accurate PET volumes as well as quantitative voxel intensities for dose painting. Issues of maintaining similar camera performance will be challenging, in particular for multi-centre trials involving response assessment. Furthermore, PET scanner technology is rapidly evolving at the current time. For example, time-of-flight scanners are now available. These changes are going to result in changes in image quality and quantitative accuracy, which may impact upon comparisons between institutions using different scanners and scan protocols. Issues of maintaining similar camera performance are difficult because different PET scanner vendors use different detectors, energy windows, scatter correction algorithms, kilovoltage settings on the CT for attenuation correction, different reconstruction algorithms etc., indicating a need for external standardization. Also, these systems are updated over time, rendering difficult the process of continuously maintaining constancy.

Clearly, other radiotracers will be available, which may prove more relevant for radiotherapy applications in the quest to determine non-invasively the radiobiological properties of the cancer [67]. The most likely second PET tracer to be approved for cancer will be fluorothymidine (FLT), which provides a direct measure of the spatial distribution of tumour proliferative activity. Other important future tracers will be fluoromisonidazole or Copper compounds, which selectively target tumour hypoxia or perfusion. For dose painting to be feasible, many more detailed studies of tracer uptake will be required to verify consistency. Also issues of image resolution and partial volume effects will need to be addressed.

2.2.3.3. Review of existing guidance documents

There are no guideline documents that currently address the requirements of PET studies specifically for radiation oncology planning, perhaps because of the novelty of PET in radiotherapy applications compared to the other imaging modalities. One important source is the publication by Coleman et al. [68], which addresses how to optimize the use of combination PET-CT imaging systems. This manuscript addresses the inter-specialty needs to achieve best results with PET-CT, a relevant objective for all disciplines in medicine, but not catering especially to the needs of radiotherapy practice.

The National Institute of Health (NIH) supports the reference image database resource (RIDER) serving to benchmark software for response assessment including PET-CT images. Although this resource does not focus on target volume delineation for radiotherapy, it does support efforts to accurately and reproducibly segment PET-CT tumour volumes, recognizing the importance of the goal for the evaluation of therapeutic response.

An introductory review of the use of PET for radiotherapy planning is the one by Zanzonico [69] and a second giving a radiation oncologist's perspective by Grégoire [70].

2.2.3.4. Summary

PET-CT simulation in which the FDG exam is fully integrated into the treatment planning process is rapidly growing as a consequence of the increasing availability of these scanners, and of the new tracers designed to provide quantitative measures of radiobiological parameters. As this technology takes off, it will be essential that a set of common quality control practices is adopted which includes scanner hardware QA tests to ensure constant instrument performance, as well as a reproducible and well-defined patient scan protocols that address questions such as scan time post tracer injection, respiratory gating, standard reconstruction parameters etc.

Special attention should be paid to the development of a standardized procedure for the use of PET scans in the delineation of target volumes as well as for the use of PET for the evaluation of treatment response. Also guidance documentation is sparse in the use of PET-CT for radiation oncology applications, and more practical "how to" manuscripts are required.

2.2.4. Portal Imaging and Portal Dosimetry

2.2.4.1. Current Use and Future Developments

(i) Portal Imaging

Portal imaging is frequently applied to verify patient set-up with respect to the radiation beam. Generally the position of the isocentre of the beams relative to the patient's anatomy, obtained from DRRs, is verified using either the actual treatment fields or two additional orthogonal fields. If the treatment fields are used, the portal image also provides information about the correct beam aperture or positioning of the blocks. Portal films are applied to verify patient set-up during treatment. A disadvantage of the use of the film technique is its off-line character, which requires a certain amount of time before the result can be applied clinically. For this reason on-line electronic portal imaging devices (EPIDs) have been developed for acquiring megavoltage images during patient treatment as reviewed by Boyer et al. [71] and more recently by Kirby and Glendinning [72]. Megavoltage images, obtained in digital format with such a device, can then be used for further analysis. The systems most commonly used are: the fluoroscopic screen/camera-based Philips/Elekta SRI-100 and TheraView (Cablon) imager, and the Varian liquid-filled matrix ionisation chamber system. The next generation of EPIDs, using amorphous silicon (a-Si) flat panel imagers [73], is nowadays commercially available from Varian, Elekta and Siemens.

In order to apply portal imaging in the clinic, local protocols have to be established stating the frequency of portal imaging, the criteria for acceptability of observed set-up deviations, and the responsibility for making decisions for changing the patient position. If properly trained, radiation therapy technologists (RTTs) can perform these corrections under the responsibility of a radiation oncologist. For several treatment sites it has been shown that a considerable

improvement in patient set-up accuracy can be achieved by applying portal imaging. Careful analysis of the results of a portal imaging programme can trace several systematic errors such as the imperfect alignment of lasers or differences in couch sagging during CT scanning and actual patient treatment. Portal imaging may also lead to various strategies to improve treatment accuracy even further in a department, for instance with respect to patient immobilisation and patient positioning by the RTTs. Knowledge of the random and systematic uncertainties of patient set-up for a specific treatment technique can be used for the adjustment of margins for this patient group, for instance in combination with dose escalation. A detailed review on the clinical use of EPIDs for portal imaging purposes has been given by Langmack [74] and Herman et al. [75].

If the target volume is moving with respect to the bony anatomy, the position of markers inside the target volume, as observed with an EPID, can be used to adjust patient set-up. For such an application it is assumed that the position of the markers does not change during a full series of fractions, which seems to be valid for gold seeds during prostate treatment. Such an approach may give more accurate information about the actual position of the target volume than a surrogate such as the bony anatomy. Because a relatively large number of images can be made during one treatment fraction, EPIDs can in principle also be used to measure set-up variation during one treatment session. This application has, however, been explored more comprehensively using other methods of imaging.

Portal imaging systems are becoming mature. The new amorphous silicon type detectors promise significant improvement in image quality over older systems. To fully utilize a portal imaging system, it is important to use tools for quantitative analysis. Improved image analysis software, provided by the manufacturers of EPIDs, would increase the clinical use of their systems. By using protocols having well-defined decision rules it is possible to reduce systematic set-up errors with an acceptable workload.

(ii) Portal Dosimetry

The information available in a portal image can also be related to the dose delivered to the EPID. Various groups have therefore studied soon after their introduction the usefulness of EPIDs for dosimetry purposes [76-78]. EPIDs have the advantage that in principle dose information is available in a plane instead of one or a few points. *In vivo* dosimetry using such a device is therefore an attractive alternative compared to the use of TLD or diodes for the determination of exit and/or midplane dose delivery. Pre-treatment dosimetric verification of conformal beams [79] and intensity-modulated radiotherapy (IMRT) beams is another application of EPIDs [78, 80].

Before using an EPID for dosimetry purposes, a number of basic dosimetric characteristics have to be determined, such as the dose-response curve, reproducibility of the signal, temperature, dose rate and dose per pulse dependence and response variation with gantry rotation angle. The results of these measurements show that video-based systems are fast and have a good linear response [79]. These systems need, however, a relatively large correction for light scatter in the detector, which is position dependent. The matrix ionisation chamber system has a non-linear response and is relatively slow; i.e., it needs more MUs for the same signal compared with video-based systems [76]. A problem to be solved with the Si type of EPID is the “ghosting” effect, i.e., the additional signal after the irradiation has been stopped [81, 82]. As a consequence the EPID response is not completely linear with dose and dose rate. This effect might not be of great concern if only a few fields are applied but is of importance during dose verification of IMRT if a large number of segments with few MUs are given. Because a-Si EPIDs incorporate high atomic number materials, they exhibit a

disproportionately large response to low-energy photons [83]. This is reflected in a reduced sensitivity if a patient or phantom is in the beam, and an increased sensitivity at off-axis positions due to spectral changes of the photon beam. The effect can be reduced by covering the EPID with a layer of several mm of copper.

Various approaches have been reported for using portal dosimetry clinically. Some groups have reported the prediction of portal dose images using the planning CT data of patients and comparing these images with measured portal dose images [78, 79]. Other groups have proposed to back-project the energy fluence, obtained from a measured portal dose image, to the target of the accelerator and then to recalculate the patient dose distribution using a treatment planning system [84]. The transmission dose can also be back-projected directly to the patient level, either in a plane through the isocentre or in several planes, i.e., in 3-D [85].

2.2.4.2. Issues

Portal imaging systems are becoming mature. The new amorphous silicon type detectors promise significant improvement in image quality over older systems. To fully utilize a portal imaging system, it is important to use tools for quantitative analysis. Improved image analysis software, provided by the manufacturers of EPIDs, would increase the clinical use of their systems. By using protocols having well-defined decision rules it is possible to reduce systematic set-up errors with an acceptable workload.

If new complex treatment techniques are applied such as IMRT, the need for verification will increase. For such techniques, single-point detectors are not very efficient and a two-dimensional detector such as an EPID is an attractive tool for pre-treatment verification as well as for in-vivo dosimetry. If an EPID, which is attached permanently to the linear accelerator, were used for dosimetry purposes, this would not only yield dose information in a plane, but also decrease the workload compared to placing conventional dosimeters or films in/on a phantom for pre-treatment verification. Various in vivo-dosimetry approaches using EPIDs are currently under development by several groups. If these methods would result in commercial products, EPID transit dosimetry might become a very powerful tool to verify the dose delivery in an entire plane or in 3D during patient treatment.

2.2.4.3. Review of Guidance Documents

Portal imaging as part of the QA process of radiotherapy, as well as the advantages and limitations of the various detector systems and the ways they are clinically implemented, has been discussed in several textbooks, e.g., [5]. A disadvantage of some of the older types of EPID is their limited contrast and spatial resolution. Recent developments in flat-panel display technology have allowed the creation of new types of flat panel detectors for X-ray imaging, both for diagnostic purposes and for use as an EPID [73]. Characteristics of these types of EPIDs have been discussed in detail in this article.

Over the last years, EPIDs have become available in a large number of institutions to measure set-up errors. The increasing ability to measure patient set-up during treatment, in combination with the demand to reduce set-up errors in order to reduce PTV margins, has led to a growing number of studies on this topic. An overview of set-up error determination strategies using portal imaging and the results of these studies has been given by Hurkmans et al. [86]. A detailed review on the clinical use of EPIDs has been given by Langmack [74] and can be found in the report of AAPM Radiation Therapy Committee Task Group 58 [87].

In a recent study van Elmpt et al. [88] elucidated how EPIDs have contributed to the verification of the dose delivered either prior to treatment or during the actual treatment of a patient. After briefly reviewing the characteristics of the different types of EPIDs relevant for dosimetry applications, the various strategies to apply EPID dosimetry in the clinic have been summarized in that report. The current clinical practice of portal dosimetry has also been reviewed with special attention to acceptance and rejection criteria applied in the various institutions.

2.2.5. Volumetric and kV Radiographic Imaging for RT

2.2.5.1.1. Current Use, Future Developments, and Issues

The desire to escalate dose while avoiding normal tissues has placed great scrutiny on the geometric uncertainties present in the radiation therapy process. The accurate and precise placement of a conformal dose distribution within the human body is challenging due to the mobile and facile nature of the body's internal structures. To address this issue, there has been significant advancement in the development of imaging systems that reside within the radiation treatment room and provide images of internal anatomy referenced to the reference frame of the treatment unit.

There are four major imaging methods employed in the systems that are currently available on the market. These are: (i) ultrasound (US), (ii) megavoltage CT, (iii) kilovoltage radiography, and, (iv) cone-beam CT (both kilovoltage and megavoltage). These are briefly reviewed with respect to their use and future developments.

(i) Ultrasound imaging has been available for image-guidance in radiation therapy since the late 1970s [89-92]. In this approach, conventional ultrasound systems are employed in conjunction with a tracking system (optical or robotic) to allow US images of internal anatomy to be related to the isocentre of the treatment unit. The units are in broad use in the radiation therapy community with a variety of applications, but are predominantly used in localization of prostate cancer treatments. These systems have the advantages of low-cost, easy integration within the RT process, and freedom from toxicity. There continues to be some controversies. These include, the dependence of precision and accuracy on the skill and training of the operator, and the potential for errors arising from displacement of the relevant anatomy during the placement of the US probe [93, 94]. Despite these issues, there are continued improvements in the systems and new products being advanced. One manufacturer has proposed the use of US in both the simulation and treatment room to allow US-US registration to avoid the variations in interpretation associated with CT-US registration.

(ii) Megavoltage CT for image guidance has been reported in the literature for nearly two decades with early prototypes employed in both research and clinical settings [95, 96]. The development of the Tomotherapy unit has provided the ideal platform for maturation of this technology [97-99]. In the Tomotherapy approach, a fan-beam of x-rays is generated by the same system that generates the treatment beam. The transmitted fluence is detected using a conventional xenon-based CT detector array and stored for subsequent helical reconstruction. The images generated with this system are registered to the treatment unit reference image and can be employed to adjust the patient position with respect to the delivered fluence pattern. The use of the MV beam results in a loss in contrast-to-noise as compared to kilovoltage systems when equivalent doses are applied (~3 cGy to isocenter). However, the images generated are of remarkably high quality with excellent 3-D visualization of bony anatomy and some capacity for localization of soft-tissue structures such

as rectum, bladder, or lung lesions. The geometric accuracy of these images is high and should permit precise and accurate positioning of the patient. The use of the megavoltage beam provides accurate electron density estimation and reduces the magnitude of artifacts associated with metal implants. The issues facing this technology include lower spatial resolution in the longitudinal direction (typically ~3 mm), limitations on the ability to monitor motion during treatment, and the lower CNR at the megavoltage energies.

(iii) Kilovoltage radiography has seen resurgence in its use for guiding radiation therapy. Early developments [100] in these approaches carried into adaptation of kV x-ray tubes to medical linear accelerators [101]. With the exception of exotic systems being developed to support stereotactic applications [102, 103], kV systems had largely disappeared from the radiation therapy treatment room by the 1990s. Developments in x-ray detector technology enabled these systems to re-enter the field. Initial systems employed flat-panel amorphous silicon detectors mounted on the treatment table directly below the patient and paired kV x-ray tubes on the ceiling to relate the patient's bony anatomy or implanted markers to the isocentre of the treatment unit. These systems offer high geometric targeting precision and accuracy for high contrast surrogates of the target and normal tissues. The low imaging dose and high level of integration make it possible to perform multiple localizations during the course of a single fraction to verify correct and stable targeting of the treatment beam. [104, 105] The extension of these approaches to evaluate soft-tissue targeting and normal structure avoidance is difficult due to the low contrast and 3-D extent of these structures. The potential for very frequent monitoring (~15 fps) is made possible with the development of high-performance fluoroscopic modes of the amorphous silicon flat-panel detectors [106]. These approaches have the potential to allow automated tracking of fiducials (gold markers, visicoilsTM, surgical clips) or high-contrast anatomical structures (e.g., focal lung lesions) during radiation delivery. These developments are likely to be re-energized by the development of numerous kV equipped accelerators offering cone-beam CT for image-guidance purposes (see below). The major challenge with this technology is the presence of overlying anatomy in the radiographic images and the potential for registration to composite features formed by these structures.

(iv) The same technological developments that enabled the re-development of kV radiographic imaging has also allowed the creation of both kV and MV cone-beam CT volumetric approaches that readily adapt to the conventional medical linear accelerator [107-109]. In these approaches, a very high quality series of low-dose radiographs (either kV or MV) are accumulated during the rotation of the gantry (190° to 360°) about the patient. Provided appropriate mapping of the system geometry has been performed, it is possible to employ filtered back-projection methods [110] to reconstruct an x-ray cross-section map (effectively a 3-D, high resolution CT image) of the patient's internal anatomy while positioned on the couch of the treatment unit. This allows the operator to detect, localize, and adjust the location of the internal anatomy with respect to the treatment beam just before the start of irradiation. These approaches have the advantage of soft-tissue detection and imaging of the patient in the treatment position. The challenges for these approaches are numerous despite their rapid penetration into the clinical setting. It is estimated that nearly 80% of conventional accelerators being delivered to the market by major manufacturers are equipped with kV imaging capabilities (radiographic and cone-beam CT). The greatest issues facing these systems arise from intra-acquisition motion, x-ray scatter on the detectors, detector lag, and limited field of view of the x-ray detector. These lead to variable image quality, inaccuracy of CT numbers, presence of shading, and truncation artefacts. The additional dose due to the imaging is a concern and is considered in the selection of the imaging technique. For the kV systems, the geometric stability is a perceived concern due to the independence of

the kV and MV components. However, the geometric performance has been demonstrated to be highly stable through numerous studies [111]. The MV cone-beam CT systems have their merits with respect to common isocentre and avoiding the need for additional hardware. However, the presence of the treatment collimator limits the field-of-view of the imaging system to a 400 mm diameter cylinder.

The breadth of imaging technology being introduced into the radiation treatment room is remarkable. This breadth will challenge the knowledge of the staff involved in the process. The physicist will be seen as a central player in this activity with respect to addressing imaging performance, explaining artifacts, and providing evidence of the geometric accuracy. The interpretation of these images by the radiation therapist and oncologist will also require additional training. Furthermore, the quantity of images produced with these systems will shift the radiation therapy department's information technology needs quite substantially. Per patient, these systems generate at least an order of magnitude more image information than all the other imaging activities combined. This will increase the need for electronic charting and coordination of dataflow in the radiation therapy centre.

2.2.5.2. Review of Guidance Documents

While there are relatively few published guidance documents for the quality assurance and appropriate use of image-guidance technologies this is likely to change in the next few years. The AAPM Task Group Report 58 on electronic portal imaging technology (the dominant image-guidance technology in the field to this point, see section 2.3.4) was published in 2001 and provides a basis for the issues at play in image-guidance that the community can draw upon for the radiographic and volumetric methods. The components of the report that are most relevant relate to (i) the modes of using imaging technology to guide the therapy, and (ii) human resources that are necessary to support the appropriate use of the technology.

The magnitude of doses delivered in kV radiographic image-guidance has recently been reviewed by Murphy et al. in the AAPM Task Group Report 75 [106]. This report highlights the appropriate dosimetry methods and quantities to report. There is no specific utilization guidance provided with the exception of the general principle of applying the ALARA methods when considering the development of imaging techniques.

Generally, the lack of guidance documents for the appropriate use of novel image-guidance systems has been recognized and is being addressed by a number of AAPM task groups that are underway.

The long use of ultrasound imaging for IGRT without a guidance document is unfortunate. This is now being addressed through the AAPM Task Group 154 entitled "Quality Assurance of Ultrasound-Guided Radiotherapy" (Chair: Janelle Molloy). The group carries the charge:

- 1. To produce a guidance document for clinical medical physicists describing recommended quality assurance (QA) procedures for ultrasound-guided external beam radiotherapy localization.*
- 2. The task group is designed to produce a focused, fast-track report.*
- 3. Specifically, the report will:*
 - Briefly summarize the relevant literature and state of the art;*

- *briefly summarize general US imaging physics and QA considerations; describe existing commercially available systems,*
- *describe simulation, treatment planning and treatment delivery considerations in the context of the application of US localization, including patient selection;*
- *list recommended QA test procedures, frequencies and tolerances”*

This is the first task group on this technology since its broad introduction in 1997 and is long overdue.

Radiographic imaging using kilovoltage systems has inspired the creation of AAPM Task Group 104 (Chairs: F-F Yin and J.W. Wong). The charge for this group is:

- 1. Review the current existing kV x-ray systems used in the radiation treatment room, including system configurations, specifications, operation principles, and functionality.*
- 2. Discuss the current clinical application methods about how these systems could be used to improve treatment accuracy and their limitations.*
- 3. Discuss issues related to effective implementation in the routine clinical procedures.*
- 4. Discuss issues related to acceptance testing and quality assurance....”.*

This report is currently under review within the AAPM Task Group system and should be published by the end of 2008. This represents a general review of radiographic guidance on conventional medical linear accelerators.

The rapid deployment of the Tomotherapy system [98] has created demand for guidance beyond that provided by the manufacturer. Guidance documents can be found in the literature [112] and the AAPM Task Group 148 is under development with specific application to the Tomotherapy unit. It is entitled “QA for Helical Tomotherapy” (Chair: Nikos Papanikolaou) and has the following charge:

- 1. To make recommendations on quality assurance techniques, frequencies, and tolerances.*
- 2. To make recommendations on dosimetric verification techniques.*

In addition to the AAPM Task Group literature, there are other guidance documents available. These include the textbook edited by J. Van Dyk (Modern Technology of Radiation Therapy, Volume 1 &2) with a chapter dedicated to the implementation and QA of image-guided RT. In addition, Yoo et al. and Lehmann et al. have described a QA program for use with the Varian On-Board Imager (OBI) and Elekta Synergy Cone Beam CT system, respectively, in their publications [113, 114].

ESTRO has recently established a scientific organisation, the European Institute of Radiotherapy (EIR) to promote awareness, research and development in radiation oncology, and to provide an authoritative European view on newly emerging topics important to

radiation oncology. Topics to be included in these activities will be oncology research related to radiation therapy, basic biology, clinical practice issues, primary radiotherapy technology and related technology such as imaging. Potential topics for task groups (TGs) are therapy approaches using complex modalities such as hadron therapy, molecular imaging, biological modelling, (hypo)fractionation and image-guidance to improve target volume delineation and patient set-up accuracy. The topic chosen by the first TG, coordinated by Dr. Stine Korreman, was image-guided radiotherapy. The activities of the task group are to explore and evaluate the implementation of 3-D CT- based image-guided in-room systems, to contact departments to gather information about the image-guided method(s) used in their department, to collect information about two common case of head & neck cancer and prostate cancer, and to compare the work flow processes. The ultimate aim of the TG is to inform specifically people working in smaller departments involved in the purchase of such equipment in order to allow them to make the best decision based on their needs/budget/capacities. It is expected that each TG will generate a consensus statement or publishable paper in a relatively short time period (~ one year). After review it will be distributed through existing ESTRO communication channels (website, newsletter, green journal).

2.2.5.3. Summary

Overall, the use of imaging in the treatment room is expanding rapidly with a variety of technologies being introduced. These systems are critical in the therapy process, as they verify the geometric placement of the radiation distribution within the body. Furthermore, the perception in the community is that these systems are highly precise and accurate. This will tend to push the field to reliance on this precision and accuracy. The greatest risk is misplaced confidence resulting in geographical miss of the tumour and excess irradiation of the normal critical structures. Clearly, there is need for guidance on its safe and appropriate use. Organizations are in the process of developing these documents with the intention of recommending models of use and assisting the clinical practitioner in their safe and effective application.

2.2.6. Review of Guidance Documents for Serial and Multi-Modal Image use in RT

2.2.6.1. Current Use, Future Developments, and Issues

As the frequency and variety of imaging increases, associated tasks such as the registration and fusion of sequential and multimodality images is increasing. Furthermore, the increased demand requires faster solutions to be developed. Understanding the limitations of the data input, and limitations of the algorithms used for registration is important to avoid geometric errors and therefore dosimetric errors during treatment. Ensuring that the input images are acquired in the treatment position using flat couch inserts and the same immobilization devices for the different modalities is of particular importance. Careful patient alignment, including the use of lasers, will reduce the difficulty of the registration problem. MR imaging proposes a particular challenge, given the potential for geometric distortion and artifacts. AAPM Task Group 117 is developing guidelines for the use of MRI data in treatment planning and stereotactic procedures with an emphasis on spatial accuracy and quality control.

Rigid registration within and between image modalities is available on most treatment planning systems. Almost all systems offer manual registration and some offer automatic registration algorithms (mutual information, Chamfer matching etc). Often manual matching can be used for a good input to the automatic algorithm, and the results of the automatic algorithm can be adjusted manually. Guideline documents for rigid registration include Mutic

et al [115] and the use of an FRE/TRE formalism [116]. AAPM Task Group 132 is currently reviewing and preparing guidelines for the use of image registration and data fusion algorithms and techniques in radiotherapy treatment planning.

There are a number of deformable algorithms to account for intermodality registration, e.g. MR-CT and serial intramodality registration, e.g. 4-D CT and repeat CBCT. Task Group 132 as mentioned above is including the evaluation and guidelines for deformable algorithms in their charge. Deformable registration algorithms include different similarity metrics, such as mutual information and cross correlation, as well as interpolation methods such as finite element, optical flow and b-spline methods. Verifying deformable algorithms is challenging, as often there is a vector connecting the source and target image for each image voxel. There is much activity in the validation of deformable algorithms including the development of phantoms [101-102], and the validation of algorithms on these phantoms [103] and patient images [117, 118].

It is important to note that all registration algorithms have uncertainties, and these uncertainties are spatially dependent. Also, local rather than global approaches are often more appropriate in radiotherapy. For example, when registering an MR scan to a CT scan for a stereotactic spinal lesion treatment, it is more important to match the vertebrae on the two modalities than obtaining a good match over the entire volume of anatomy imaged. In such cases carefully selecting the parameters for automatic registration or performing manual registration are required.

2.3. Imaging in the Radiation Therapy Workflow

Imaging is included in the radiation therapy process in a variety of ways. The approach taken depends upon: the type of imaging, the availability of the imaging technology (directly in the radiation therapy department or in an adjacent radiology department), the clinical objective, and, and the presence of other imaging modalities. The variation in imaging workflow in RT is illustrated below.

2.3.1. CT Imaging in Radiotherapy Workflow

CT images are utilized for pre-treatment imaging, treatment planning and treatment verification for almost all 3-D conformal and IMRT treatments – see Figure 1. Many centres are predominantly or exclusively performing 2-D radiotherapy using conventional simulator based

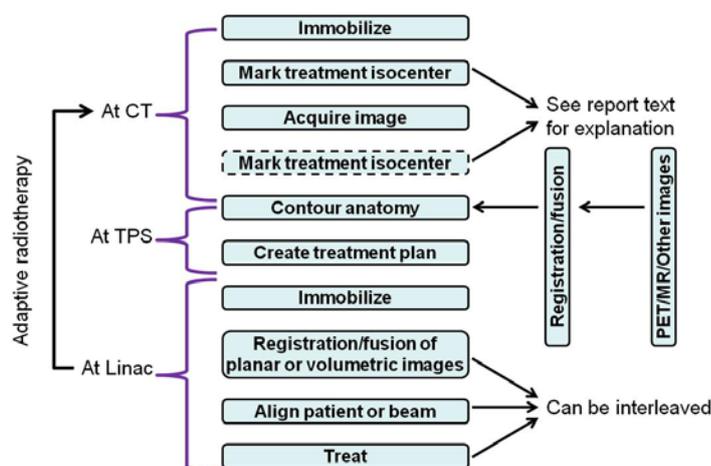


Figure 1. Workflow for CT-based radiotherapy.

verification and the introduction of CT-based radiotherapy has significant implications for workflow. The IAEA is developing a TECDOC for this transition from 2-D to 3-D and IMRT.

CT scans for radiotherapy can be acquired with a CT scanner dedicated to radiation oncology, or shared with other resources, particularly radiology. Dedicated CT scanners for radiation oncology typically have fixed flat couch inserts, immediately available immobilization devices, lasers and software for CT simulation and a schedule controlled by radiation oncology that accommodates the increased time for CT simulations compared with CT scanning alone. When a CT scanner is a shared resource, a flat couch insert and immobilization devices need to be available. There may not be lasers for virtual simulation, and there can be time pressures. Whether a scanner is dedicated or shared, CT images and the isocenter position are imported into the treatment planning system. Depending on workflow and equipment, volume segmentation of tumor and normal anatomy, and margin assignment, can be performed with CT simulation software, or by the treatment planning system. Volume delineation can also be assisted through images from other modalities, including MR and PET – see Figure 2. Once a treatment plan has been created, digitally reconstructed radiographs (DRRs) are computed if planar imaging is to be performed for verification in the treatment room. These DRRs can either be from the treatment beam angles or from an orthogonal

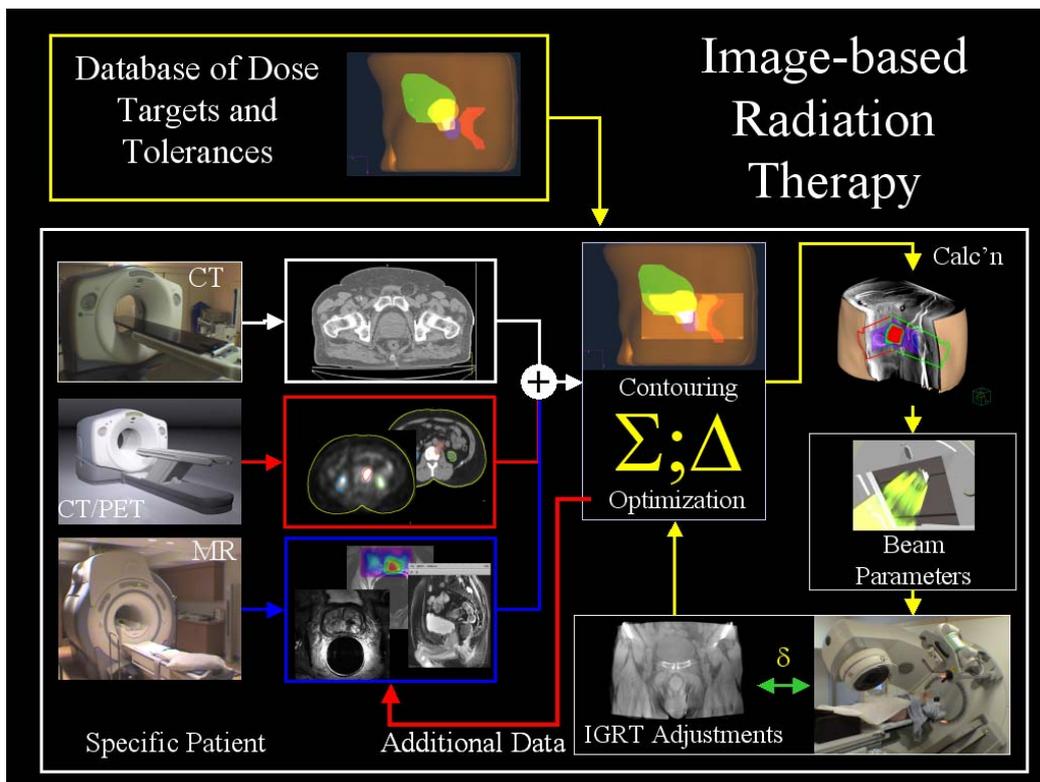


image pair.

Figure 2: Progression of the radiation therapy workflow towards an image-informed process, in which images from a variety of sources are used in the design of the therapy. These images are registered (see +) and fused for visualization and manual or automated segmentation. The use of these images requires a strong understanding of the origin of the image signal and verification that this signal is faithfully transferred through to the planning and delivery components. Imaging in the room is now being more broadly employed to both evaluate the radiation delivered (portal dosimetry) and geometric targeting (e.g., cone-beam CT, Tomotherapy, US).

Once a treatment plan has been approved, the plan, isocenter and DRRs or CT scan itself (for 2-D to 3-D matching) are sent to the linear accelerator. DRRs are used for comparison with megavoltage or kilovoltage planar images for appropriate patient alignment. The CT scan is used to estimate appropriate patient alignment by registration and fusion of the CT scan with volumetric images acquired at the linear accelerator which can be kilovoltage or megavoltage, cone beam or fan beam. CT images pervade the entire workflow of 3-D conformal and IMRT treatments. Appropriate staffing, protocols for use and quality assurance are required to safely implement CT-based treatments.

2.3.2. PET and SPECT for Target Definition RT

PET and SPECT provide functional information on tumour behaviour, and may also identify the extent and location of active disease. Depending on local equipment and local practice, CT may be integrated into the radionuclide examination, facilitating localization of disease and also enabling local CT simulation of treatment and acquisition of morphological CT planning scans. Target identification will be best performed in conjunction with imaging staff. Scans may be performed prior to treatment for planning, during treatment to adjust target volumes, after treatment to assess response and identify recurrence.

Image information for radiotherapy treatment planning may be acquired in the following ways:

- Areas of active disease may be transferred visually to CT based treatment planning.
- Areas of active disease may be integrated with CT and transferred to plans based on a separate CT simulation session.
- PET/CT or SPECT/CT may be performed in the treatment position with appropriate patient set-up procedures, with CT simulation performed on the same device prior to transfer to planning.
- Where diagnostic radionuclide scanning is performed separately to a planning radionuclide/CT scan, it may be possible to rescan the patient for a radionuclide planning scan utilizing the same radionuclide dose.

Transfer of radionuclide derived data for planning use may require registration, and steps to assure spatial fidelity. Imaging should follow a pre-determined protocol, and the location and extent of disease should be determined on the basis of an established evaluation protocol, with appropriate input from radionuclide staff.

2.3.3. Processes for MR Image Use in Planning and Response

MR image data can be used to inform the planning process in several ways. Currently morphological data from MR based on T1, T2 and similarly weighted images, together with contrast agents can be used to define tumour and organ extent. There is growing use of functional and metabolic information to complement morphological images. These data are used in a number of ways:

- Data can be transferred visually onto CT based plans.
- Data can be digitally transferred to a planning system and co-registered with CT – with and without prior distortion correction.

- Data can be used directly for planning after distortion correction and with bulk assignment of attenuation corrections (MR simulation).

MR simulation requires appropriate set up of the patient in the treatment position, registration of surface markers, and assurance of spatial fidelity. Registration to CT also benefits from these steps. MR may also be used to assess changes in target volume during therapy and to assess response and residual disease following treatment. MR sessions need to be booked for appropriate times prior to and during therapy, using an established protocol, ensuring appropriate expertise is available for set-up and evaluation, and that planning software can receive and handle the required types of MR data.

2.3.4. On-line and Off-line Analysis for In-room Image Guidance

After the technical development and optimization of in-room imaging tools integrated with the actual treatment process, the next important step is the development and implementation of clinical protocols for image-based guidance. Currently there is information available in the literature describing such protocols for portal imaging, but to date few articles have been published for other in-room imaging methods. Therefore, these protocols have to be developed, or adapted from portal imaging experience, which will be a topic of interest for the coming years.

The information available on the clinical use of electronic portal imaging can be separated into off-line and on-line applications. Off-line analysis has been used to quantify and separate random and systematic uncertainties for individual patients. This information can be used to design decision rules to indicate when to correct a set-up deviation for a particular type of treatment, *e.g.*, [119]. Off-line set-up verification protocols can be based on decision rules using a shrinking action level (SAL) [120]. Other approaches are based on average deviations observed during the first number of fractions and assuming these deviations are valid for the whole treatment, *e.g.* the no-action level (NAL) protocol [121]. The same approaches can be applied for other in-room imaging data driven, for instance, by 3-D *bony anatomy* registration to the planning CT data. Additionally, *soft tissue* driven off-line correction protocols have to be implemented, for instance for prostate, lung and bladder cancer treatments. Furthermore, adaptive radiotherapy (ART) protocols [122] have to be developed. By using image information obtained during the first week of treatment, the PTV margin can be adapted for an individual patient. A new plan can then be designed using the average GTV and OAR positions. In the following weeks, new scans are used to monitor the adequacy of the ART treatment plan. It should be noted that the clinically applied GTV-to-PTV margins should compensate for all geometrical uncertainties in the radiotherapy chain including those induced by target definition, which are not improved by in-room image guidance.

EPIDs and other modern in-room imaging tools profit from the availability of fast and user-friendly software for image analysis. An advantage of on-line analysis compared with off-line analysis is that the image is available a few seconds after the start of the irradiation. This allows, in principle, a quick decision to terminate the treatment if the comparison of such an image with the simulator image or DRR does not show unacceptable discrepancies. On-line correction protocols are therefore of particular importance for set-up verification if only a few fractions are applied, *e.g.*, during hypo-fractionated treatments.

Radiotherapy technicians generally perform the acquisition of in-room images. The evaluation of these data can also be performed by them if they are properly trained in applying the special registration software tools, using protocols having well defined criteria for acceptability of (small) patient set-up deviations. These protocols should be developed in

close cooperation with radiation oncologists and physicists, dividing also the responsibilities for making clinical decisions. This is an area that requires significant attention and will stress the need for continuously revised curricula and inter-professional relations if the image information is to be fully exploited.

2.3.5. Staff Training for Imaging in Radiotherapy

Imaging plays a central and increasingly important role in radiotherapy. It has been observed that acquisitions of new technology in Member States often represent a massive change of capabilities and that staff is generally not appropriately educated to manage the safe and optimal use of the new technology. Often the new technology has emerged after most of the current staff completed their formal training and therefore do not have an in-depth understanding of the emerging technology. Therefore appropriate and relevant training of physicists, radiation oncologists and radiation therapists on the aspects of imaging in radiotherapy is needed.

Current training curricula and textbooks do not reflect the central role and importance of imaging in radiotherapy. More over, the use of imaging is rapidly increasing with time and it is expected that this increase will continue to evolve and demand an ongoing continuous learning effort by the entire treatment team. Training curricula for medical physicists, radiation oncologists and radiation technologists have been slow to adapt and incorporate the growing role of imaging in radiotherapy. Curricula, certification and recertification should be revised to include appropriate training and competencies for the use of imaging in radiotherapy.

The additional complexity and tasks associated with imaging in radiotherapy mean that staffing levels need to be increased appropriately. Even the additional training requires a substantial time commitment for all personnel involved in the process. The appropriate increased staffing levels required to safely include imaging into the practice of radiotherapy is not clearly quantified. The IAEA should proactively seek to determine and provide guidance on appropriate staffing levels.

Radiology, nuclear medicine and other departments have expertise in imaging. Collaborating with departments with imaging expertise, and where available didactic courses, such as courses taught to medical residents and trainees in radiology, should be taken advantage of by the radiation oncology professionals.

In the recommendations section are several proposed mechanisms for increasing the education and appropriate use of imaging in radiotherapy. These include exchanges, hands-on teaching courses and web-based training.

Important areas of education on the role of imaging in radiotherapy include, but are not limited to:

- Understanding of the sources, applications, and magnitudes of geometrical variations and uncertainties of imaging in radiotherapy.
- Appropriate interpretation of images and factors generating image signal.
- Understanding the workflow and appropriate quality assurance of the various subprocesses of imaging in radiotherapy.
- Patient immobilization and isocenter marking.
- Rigid and deformable image registration methods and limitations.

- Segmentation of tumour and normal anatomy on volumetric images from multimodal sources.
- Treatment planning using 3-D, 4-D and multimodality information.
- Appropriate understanding of the sources of errors and error management to guide margin definition.
- Evaluation and assessment of images acquired within the treatment room.
- Image acquisition, registration and appropriate use during the treatment process.
- Verification of radiation treatments.
- Information technology requirements to manage the increase in imaging during the treatment process.

Note: the choice of topics and depth of topics will vary with the professional responsibilities of the medical physicist, radiation oncologist and radiation technologist.

Throughout the report, resources for training in particular areas are given. Some general resources for imaging in radiotherapy include an NCI-supported dosimetry training tool⁷ and EMERALD, a European Union initiative⁸; however these resources could be expanded to emphasize the role of imaging in radiotherapy. There are several organizations, including the AAPM, ASTRO, and ESTRO developing guideline documents for topics associated with imaging in radiotherapy. In particular, AAPM Task Group 131 is actively developing resources for medical physics training in developing countries.

2.3.6. Data Handling and Information Technologies

The growing use of imaging is resulting in a substantial demand on the data communication and storage systems of the radiation therapy department. Modern radiation therapy practice is moving toward a highly integrated electronic patient chart for executing, recording and, verifying the radiation treatments. This has allowed the field to pursue advanced methods of treatment such as IMRT, in which hundreds of parameters are used to specify the treatment machine operation. Clearly, this could not have been initiated without digital communication methods. The efficient use of imaging will also rely this infrastructure with greater and greater levels of integration foreseeable in the near future.

The creation of the DICOM standard has been an important step in allowing these developments to move from the academic centres to the community at large. The DICOM standard, which is still evolving, is now paying dividends for the community by streamlining workflow and allowing developments of third party tools within the radiation therapy market. There are numerous outstanding issues related to ‘non-standard image workflows’. While radiation therapy employs significant numbers of images, it is not a workflow that has been as well developed as the conventional diagnostic workflow. As a result, it is not uncommon to find that image sets of non-standard orientation are not accurately reformatted when carried into the radiation therapy environment. The community is addressing this issue through the Radiation Oncology domain of the IHE (Integrating the Healthcare Enterprise, www.ihe.net, and IHE-RO - http://www.ihe.net/Technical_Framework/index.cfm#rad_onc).

The quantity of imaging data (in Mb) being generated continues to climb from both a demand for higher resolution imaging (1, 4, 16, and 64 slice CT) and the development of volumetric imaging in the treatment room. It is likely that the volumetric imaging in the treatment room

⁷ <http://dosimetrytrainingtool.com/>

⁸ <http://www.emerald2.eu/>

will generate ~95% of the entire radiotherapy related patient storage requirements. This is related directly to the number of fractions used to deliver the total radiation dose (e.g., 20 fractions with volumetric imaging for every planning dataset). Restated, the storage demands of the department will increase by a factor of 20. Outstanding issues include the lack of direction regarding the long-term storage needs for planning and guidance images (for both patient re-planning and legal issues). The development of rational guidelines will serve to reduce the cost of these systems as they mature over the next several years.

REFERENCES

- [1] INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS, ICRU Report 50: Prescribing, Recording, and Reporting Photon Beam Therapy., ICRU, Bethesda (1993).
- [2] INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS, ICRU Report 62: Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50) ICRU, Bethesda (1999).
- [3] LETOURNEAU, D., et al., Online planning and delivery technique for radiotherapy of spinal metastases using cone-beam CT: image quality and system performance, *Int J Radiat Oncol Biol Phys* **67** 4 (2007) 1229-37.
- [4] MUTIC, S., et al., Quality assurance for computed-tomography simulators and the computed-tomography-simulation process: report of the AAPM Radiation Therapy Committee Task Group No. 66, *Med Phys* **30** 10 (2003) 2762-92.
- [5] PODGORSK, E.B., editor, *Radiation Oncology Physics: A Handbook for Teachers and Students*, 2005, Vienna (2005).
- [6] IPEM, Report 81: Physics aspects of quality control in radiotherapy, York (1999).
- [7] KEALL, P.J., et al., The management of respiratory motion in radiation oncology report of AAPM Task Group 76, *Med Phys* **33** 10 (2006) 3874-900.
- [8] KEALL, P.J., "4D Treatment Planning", *Image-guided IMRT*, (BORTFELD, T., SCHMIDT-ULLRICH, R.K., DENEVE, W.WAZER, D.E., Eds), Springer-Verlag, Heidelberg, (2005) 259-267.
- [9] D'ARCY, J.A., et al., Informatics in Radiology (infoRAD): Magnetic Resonance Imaging Workbench: analysis and visualization of dynamic contrast-enhanced MR imaging data, *Radiographics* **26** 2 (2006) 621-32.
- [10] LEACH, M.O., et al., The assessment of antiangiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations, *Br J Cancer* **92** 9 (2005) 1599-610.
- [11] PAYNE, G.S., LEACH, M.O., Applications of magnetic resonance spectroscopy in radiotherapy treatment planning, *Br J Radiol* **79 Spec No 1** (2006) S16-26.
- [12] KHOO, V.S., et al., Comparison of MRI with CT for the radiotherapy planning of prostate cancer: a feasibility study, *Br J Radiol* **72** 858 (1999) 590-7.
- [13] NEWBOLD, K., et al., Advanced imaging applied to radiotherapy planning in head and neck cancer: a clinical review, *Br J Radiol* **79** 943 (2006) 554-61.
- [14] MIZOWAKI, T., COHEN, G.N., FUNG, A.Y., ZAIDER, M., Towards integrating functional imaging in the treatment of prostate cancer with radiation: the registration of the MR spectroscopy imaging to ultrasound/CT images and its implementation in treatment planning, *Int J Radiat Oncol Biol Phys* **54** 5 (2002) 1558-64.
- [15] PADHANI, A.R., et al., Evaluating the effect of rectal distension and rectal movement on prostate gland position using cine MRI, *Int J Radiat Oncol Biol Phys* **44** 3 (1999) 525-33.
- [16] GARCIA-ALVAREZ, R., LINEY, G.P., BEAVIS, A.W., Repeatability of functional MRI for conformal avoidance radiotherapy planning, *J Magn Reson Imaging* **23** 2 (2006) 108-14.
- [17] HABERG, A., KVISTAD, K.A., UNSGARD, G., HARALDSETH, O., Preoperative blood oxygen level-dependent functional magnetic resonance imaging in patients with primary brain tumors: clinical application and outcome, *Neurosurgery* **54** 4 (2004) 902-14; discussion 914-5.
- [18] NUCIFORA, P.G., VERMA, R., LEE, S.K., MELHEM, E.R., Diffusion-tensor MR imaging and tractography: exploring brain microstructure and connectivity, *Radiology* **245** 2 (2007) 367-84.

- [19] MARUYAMA, K., et al., Integration of three-dimensional corticospinal tractography into treatment planning for gamma knife surgery, *J Neurosurg* **102** 4 (2005) 673-7.
- [20] PARMAR, H., SITO, Y.Y., YEO, T.T., Combined magnetic resonance tractography and functional magnetic resonance imaging in evaluation of brain tumors involving the motor system, *J Comput Assist Tomogr* **28** 4 (2004) 551-6.
- [21] PADHANI, A.R., KROHN, K.A., LEWIS, J.S., ALBER, M., Imaging oxygenation of human tumours, *Eur Radiol* **17** 4 (2007) 861-72.
- [22] SEDDON, B.M., et al., A phase I study of SR-4554 via intravenous administration for noninvasive investigation of tumor hypoxia by magnetic resonance spectroscopy in patients with malignancy, *Clin Cancer Res* **9** 14 (2003) 5101-12.
- [23] PARTRIDGE, M., et al., An investigation of dose calculation accuracy in intensity-modulated radiotherapy of sites in the head & neck, *Phys Med* **22** 3 (2006) 97-104.
- [24] WATANABE, Y., AKIMITSU, T., HIROKAWA, Y., MOOIJ, R.B., PERERA, G.M., Evaluation of dose delivery accuracy of Gamma Knife by polymer gel dosimetry, *J Appl Clin Med Phys* **6** 3 (2005) 133-42.
- [25] MIZOWAKI, T., et al., Development of an MR simulator: experimental verification of geometric distortion and clinical application, *Radiology* **199** 3 (1996) 855-60.
- [26] MAH, D., et al., Characteristics and quality assurance of a dedicated open 0.23 T MRI for radiation therapy simulation, *Med Phys* **29** 11 (2002) 2541-7.
- [27] LEE, Y.K., et al., Radiotherapy treatment planning of prostate cancer using magnetic resonance imaging alone, *Radiother Oncol* **66** 2 (2003) 203-16.
- [28] IPEM, Report 80: Quality control in magnetic resonance imaging., IPEM, York (1995).
- [29] AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE, Quality Assurance. Methods and Phantoms for Magnetic Resonance Imaging., AAPM, Maryland (1990).
- [30] PRICE, R.R., et al., Quality assurance methods and phantoms for magnetic resonance imaging: report of AAPM nuclear magnetic resonance Task Group No. 1, *Med Phys* **17** 2 (1990) 287-95.
- [31] OCH, J.G., CLARKE, G.D., SOBOL, W.T., ROSEN, C.W., MUN, S.K., Acceptance testing of magnetic resonance imaging systems: report of AAPM Nuclear Magnetic Resonance Task Group No. 6, *Med Phys* **19** 1 (1992) 217-29.
- [32] LERSKI, R.A., ORR, J.S., "Practical testing", *Practical NMR Imaging*, (FOSTER, M.A., HUTCHINSON, J.M.S., Ed.), IRL Press, Oxford, (1987) 81-93.
- [33] MEDICAL DEVICES DIRECTORATE, Evaluation report no. 47: Assessment of the Imaging Performance of the Siemens Magnetom 63 SP 400 1.5T MR Imaging System., HMSO, London (1992).
- [34] PURDY, D., "Acceptance testing of magnetic resonance imagers: Which tests are worthwhile? MRI: Acceptance testing and quality control - the role of the clinical medical physicist." *Proceedings of an AAPM Symposium (Proc. Conf. Maryland, 1988)*, AAPM.
- [35] SANO, R., "NEMA Standards: Performance Standards for Clinical Magnetic Resonance systems." *MRI: Acceptance Testing and Quality Control - The Role of the Clinical Medical Physicist. (Proc. Conf. Maryland, 1988)*, AAPM.
- [36] BARKER, G.J., TOFTS, P.S., Semiautomated quality assurance for quantitative magnetic resonance imaging, *Magn Reson Imaging* **10** 4 (1992) 585-95.
- [37] FIRBANK, M.J., HARRISON, R.M., WILLIAMS, E.D., COULTHARD, A., Quality assurance for MRI: practical experience, *Br J Radiol* **73** 868 (2000) 376-83.
- [38] CHEN, C.C., WAN, Y.L., WAI, Y.Y., LIU, H.L., Quality assurance of clinical MRI scanners using ACR MRI phantom: preliminary results, *J Digit Imaging* **17** 4 (2004) 279-84.

- [39] WALKER, P., LERSKI, R.A., MATHUR-DE VRE, R., BINET, J., YANE, F., Preparation of agarose gels as reference substances for NMR relaxation time measurement. EEC Concerted Action Program, *Magn Reson Imaging* **6** 2 (1988) 215-22.
- [40] KHOO, V.S., et al., Magnetic resonance imaging (MRI): considerations and applications in radiotherapy treatment planning, *Radiother Oncol* **42** 1 (1997) 1-15.
- [41] MOORE, C.S., LINEY, G.P., BEAVIS, A.W., Quality assurance of registration of CT and MRI data sets for treatment planning of radiotherapy for head and neck cancers, *J Appl Clin Med Phys* **5** 1 (2004) 25-35.
- [42] KOCH, N., LIU, H.H., OLSSON, L.E., JACKSON, E.F., Assessment of geometrical accuracy of magnetic resonance images for radiation therapy of lung cancers, *J Appl Clin Med Phys* **4** 4 (2003) 352-64.
- [43] BEDNARZ, G., DOWNES, M.B., CORN, B.W., CURRAN, W.J., GOLDMAN, H.W., Evaluation of the spatial accuracy of magnetic resonance imaging-based stereotactic target localization for gamma knife radiosurgery of functional disorders, *Neurosurgery* **45** 5 (1999) 1156-61; discussion 1161-3.
- [44] HECK, B., JESS-HEMPEN, A., KREINER, H.J., SCHOPGENS, H., MACK, A., Accuracy and stability of positioning in radiosurgery: long-term results of the Gamma Knife system, *Med Phys* **34** 4 (2007) 1487-95.
- [45] MACK, A., CZEMPIEL, H., KREINER, H.J., DURR, G., WOWRA, B., Quality assurance in stereotactic space. A system test for verifying the accuracy of aim in radiosurgery, *Med Phys* **29** 4 (2002) 561-8.
- [46] PAPAGIANNIS, P., et al., Three-dimensional dose verification of the clinical application of gamma knife stereotactic radiosurgery using polymer gel and MRI, *Phys Med Biol* **50** 9 (2005) 1979-90.
- [47] RAHIMIAN, J., et al., Geometrical accuracy of the Novalis stereotactic radiosurgery system for trigeminal neuralgia, *J Neurosurg* **101 Suppl 3** (2004) 351-5.
- [48] SCHEIB, S.G., GIANOLINI, S., LOMAX, N.J., MACK, A., High precision radiosurgery and technical standards, *Acta Neurochir Suppl* **91** (2004) 9-23.
- [49] WALTON, L., HAMPSHIRE, A., FORSTER, D.M., KEMENY, A.A., A phantom study to assess the accuracy of stereotactic localization, using T1-weighted magnetic resonance imaging with the Leksell stereotactic system, *Neurosurgery* **38** 1 (1996) 170-6; discussion 176-8.
- [50] FINNIGAN, D.J., TANNER, S.F., DEARNALEY, D.P., EDSER, E., HORWICH, A., LEACH, M.O., MAYLES, W.P.M., "Distortion-corrected magnetic resonance images for pelvic radiotherapy treatment planning." *Quantitative Imaging in Oncology. Proceedings of the 19th LH Gray Conference April 1995.*, (FAULKNER, K., CAREY, B., CRELLIN, A., HARRISON, R.M., Ed.), British Institute of Radiology, London, (1996) 71-75.
- [51] CHEN, Z., et al., Investigation of MR image distortion for radiotherapy treatment planning of prostate cancer, *Phys Med Biol* **51** 6 (2006) 1393-403.
- [52] DORAN, S.J., CHARLES-EDWARDS, L., REINSBERG, S.A., LEACH, M.O., A complete distortion correction for MR images: I. Gradient warp correction, *Phys Med Biol* **50** 7 (2005) 1343-61.
- [53] REINSBERG, S.A., DORAN, S.J., CHARLES-EDWARDS, E.M., LEACH, M.O., A complete distortion correction for MR images: II. Rectification of static-field inhomogeneities by similarity-based profile mapping, *Phys Med Biol* **50** 11 (2005) 2651-61.
- [54] TANNER, S.F., et al., Radiotherapy planning of the pelvis using distortion corrected MR images: the removal of system distortions, *Phys Med Biol* **45** 8 (2000) 2117-32.

- [55] MUTIC, S., et al., Multimodality image registration quality assurance for conformal three-dimensional treatment planning, *Int J Radiat Oncol Biol Phys* **51** 1 (2001) 255-60.
- [56] DE BRABANDERE, M., KIRISITS, C., PEETERS, R., HAUSTERMANS, K., VAN DEN HEUVEL, F., Accuracy of seed reconstruction in prostate postplanning studied with a CT- and MRI-compatible phantom, *Radiother Oncol* **79** 2 (2006) 190-7.
- [57] BOVEE, W.M., KEEVIL, S.F., LEACH, M.O., PODO, F., Quality assessment in in vivo NMR spectroscopy: II. A protocol for quality assessment. EEC Concerted Research Project, *Magn Reson Imaging* **13** 1 (1995) 123-9.
- [58] KEEVIL, S.F., et al., Quality assessment in in vivo NMR spectroscopy: IV. A multicentre trial of test objects and protocols for performance assessment in clinical NMR spectroscopy, *Magn Reson Imaging* **13** 1 (1995) 139-57.
- [59] LEACH, M.O., et al., Quality assessment in in vivo NMR spectroscopy: III. Clinical test objects: design, construction, and solutions, *Magn Reson Imaging* **13** 1 (1995) 131-7.
- [60] LING, C.C., LI, X.A., Over the next decade the success of radiation treatment planning will be judged by the immediate biological response of tumor cells rather than by surrogate measures such as dose maximization and uniformity, *Med Phys* **32** 7 (2005) 2189-92.
- [61] SOLBERG, T.D., AGAZARYAN, N., GOSS, B.W., DAHLBOM, M., LEE, S.P., A feasibility study of 18F-fluorodeoxyglucose positron emission tomography targeting and simultaneous integrated boost for intensity-modulated radiosurgery and radiotherapy, *J Neurosurg* **101 Suppl 3** (2004) 381-9.
- [62] VAN BAARDWIJK, A., et al., The current status of FDG-PET in tumour volume definition in radiotherapy treatment planning, *Cancer Treat Rev* **32** 4 (2006) 245-60.
- [63] WEBER, W.A., WIEDER, H., Monitoring chemotherapy and radiotherapy of solid tumors, *Eur J Nucl Med Mol Imaging* **33 Suppl 1** (2006) 27-37.
- [64] BLACK, Q.C., et al., Defining a radiotherapy target with positron emission tomography, *Int J Radiat Oncol Biol Phys* **60** 4 (2004) 1272-82.
- [65] ERDI, Y.E., et al., Segmentation of lung lesion volume by adaptive positron emission tomography image thresholding, *Cancer* **80** 12 Suppl (1997) 2505-9.
- [66] DAISNE, J.F., et al., Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen, *Radiology* **233** 1 (2004) 93-100.
- [67] LUCIGNANI, G., JERECZEK-FOSSA, B.A., ORECCHIA, R., The role of molecular imaging in precision radiation therapy for target definition, treatment planning optimisation and quality control, *Eur J Nucl Med Mol Imaging* **31** 8 (2004) 1059-63.
- [68] COLEMAN, R.E., et al., Concurrent PET/CT with an integrated imaging system: intersociety dialogue from the Joint Working Group of the American College of Radiology, the Society of Nuclear Medicine, and the Society of Computed Body Tomography and Magnetic Resonance, *J Am Coll Radiol* **2** 7 (2005) 568-84.
- [69] ZANZONICO, P., PET-based biological imaging for radiation therapy treatment planning, *Crit Rev Eukaryot Gene Expr* **16** 1 (2006) 61-101.
- [70] GREGOIRE, V., HAUSTERMANS, K., GEETS, X., ROELS, S., LONNEUX, M., PET-based treatment planning in radiotherapy: a new standard?, *J Nucl Med* **48 Suppl 1** (2007) 68S-77S.
- [71] BOYER, A.L., et al., A review of electronic portal imaging devices (EPIDs), *Med Phys* **19** 1 (1992) 1-16.
- [72] KIRBY, M.C., GLENDINNING, A.G., Developments in electronic portal imaging systems, *Br J Radiol* **79 Spec No 1** (2006) S50-65.

- [73] ANTONUK, L.E., Electronic portal imaging devices: a review and historical perspective of contemporary technologies and research, *Phys Med Biol* **47** 6 (2002) R31-65.
- [74] LANGMACK, K.A., Portal imaging, *Br J Radiol* **74** 885 (2001) 789-804.
- [75] HERMAN, M.G., Clinical use of electronic portal imaging, *Semin Radiat Oncol* **15** 3 (2005) 157-67.
- [76] BOELLAARD, R., VAN HERK, M., UITERWAAL, H., MIJNHEER, B., First clinical tests using a liquid-filled electronic portal imaging device and a convolution model for the verification of the midplane dose, *Radiother Oncol* **47** 3 (1998) 303-12.
- [77] MCNUTT, T.R., MACKIE, T.R., RECKWERDT, P., PAPANIKOLAOU, N., PALIWAL, B.R., Calculation of portal dose using the convolution/superposition method, *Med Phys* **23** 4 (1996) 527-35.
- [78] PASMA, K.L., KROONWIJK, M., DE BOER, J.C., VISSER, A.G., HEIJMEN, B.J., Accurate portal dose measurement with a fluoroscopic electronic portal imaging device (EPID) for open and wedged beams and dynamic multileaf collimation, *Phys Med Biol* **43** 8 (1998) 2047-60.
- [79] NIJSTEN, S.M., MINKEN, A.W., LAMBIN, P., BRUINVIS, I.A., Verification of treatment parameter transfer by means of electronic portal dosimetry, *Med Phys* **31** 2 (2004) 341-7.
- [80] VAN ESCH, A., DEPUYDT, T., HUYSKENS, D.P., The use of an aSi-based EPID for routine absolute dosimetric pre-treatment verification of dynamic IMRT fields, *Radiother Oncol* **71** 2 (2004) 223-34.
- [81] MCDERMOTT, L.N., et al., Comparison of ghosting effects for three commercial a-Si EPIDs, *Med Phys* **33** 7 (2006) 2448-51.
- [82] SIEWERDSEN, J.H., JAFFRAY, D.A., A ghost story: spatio-temporal response characteristics of an indirect-detection flat-panel imager, *Med Phys* **26** 8 (1999) 1624-41.
- [83] GREER, P.B., Correction of pixel sensitivity variation and off-axis response for amorphous silicon EPID dosimetry, *Med Phys* **32** 12 (2005) 3558-68.
- [84] RENNER, W.D., SARFARAZ, M., EARL, M.A., YU, C.X., A dose delivery verification method for conventional and intensity-modulated radiation therapy using measured field fluence distributions, *Med Phys* **30** 11 (2003) 2996-3005.
- [85] LOUWE, R.J., et al., Three-dimensional dose reconstruction of breast cancer treatment using portal imaging, *Med Phys* **30** 9 (2003) 2376-89.
- [86] HURKMANS, C.W., REMEIJER, P., LEBESQUE, J.V., MIJNHEER, B.J., Set-up verification using portal imaging; review of current clinical practice, *Radiother Oncol* **58** 2 (2001) 105-20.
- [87] HERMAN, M.G., et al., Clinical use of electronic portal imaging: report of AAPM Radiation Therapy Committee Task Group 58, *Med Phys* **28** 5 (2001) 712-37.
- [88] VAN ELMPT, W., MCDERMOTT, L.N., NIJSTEN, S., WENDLING, M., LAMBIN, P., MIJNHEER, B.J., Electronic portal imaging for radiotherapy dosimetry: review of current practice, *Radiother. Oncol.* (2008) in press
- [89] BADCOCK, P.C., Ultrasound scanning in the radiotherapy department, *Clin Radiol* **28** 3 (1977) 287-293.
- [90] BRASCHO, D.J., Tumor localization and treatment planning with ultrasound, *Cancer* **39** 2 Suppl (1977) 697-705.
- [91] HOLUPKA, E.J., KAPLAN, I.D., BURDETTE, E.C., SVENSSON, G.K., Ultrasound image fusion for external beam radiotherapy for prostate cancer, *Int J Radiat Oncol Biol Phys* **35** 5 (1996) 975-84.
- [92] LATTANZI, J., et al., A comparison of daily CT localization to a daily ultrasound-based system in prostate cancer, *Int J Radiat Oncol Biol Phys* **43** 4 (1999) 719-25.

- [93] ARTIGNAN, X., et al., Online ultrasound image guidance for radiotherapy of prostate cancer: impact of image acquisition on prostate displacement, *Int J Radiat Oncol Biol Phys* **59** 2 (2004) 595-601.
- [94] VAN DEN HEUVEL, F., et al., Independent verification of ultrasound based image-guided radiation treatment, using electronic portal imaging and implanted gold markers, *Med Phys* **30** 11 (2003) 2878-87.
- [95] BRAHME, A., LIND, B., NAFSTADIUS, P., Radiotherapeutic computed tomography with scanned photon beams, **13** 1 (1987) 95.
- [96] SWINDELL, W., SIMPSON, R.G., OLESON, J.R., CHEN, C.T., GRUBBS, E.A., Computed tomography with a linear accelerator with radiotherapy applications, **10** 4 (1983) 416.
- [97] MACKIE, T.R., et al., Tomotherapy, *Semin Radiat Oncol* **9** 1 (1999) 108-17.
- [98] MACKIE, T.R., et al., Tomotherapy: a new concept for the delivery of dynamic conformal radiotherapy, *Medical Physics* **20** (1993) 1709.
- [99] RUCHALA, K.J., OLIVERA, G.H., SCHLOESSER, E.A., MACKIE, T.R., Megavoltage CT on a tomotherapy system, *Phys Med Biol* **44** 10 (1999) 2597-621.
- [100] JOHNS, H.E.A.C., J. R.. A precision cobalt 60 unit for fixed field and rotation therapy, *Amer.J.Roentgenol.* **81** (1959) 4-12.
- [101] BIGGS, P.J., GOITEIN, M., AND RUSSELL, M. D., A diagnostic X ray field verification device for a 10 MV linear accelerator, *Int.J.Radiat.Oncol.Biol.Phys.* **11** 3 (1985) 635-643.
- [102] UEMATSU, M., et al., Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience, *Cancer* **82** 6 (1998) 1062-70.
- [103] SHIRATO, H., SHIMIZU, S., SHIMIZU, T., NISHIOKA, T., MIYASAKA, K., Real-time tumour-tracking radiotherapy, **353** 9161 (1999) 1331.
- [104] ADLER, J.R., JR., et al., The Cyberknife: a frameless robotic system for radiosurgery, **69** 1-4 Pt 2 (1997) 124.
- [105] MURPHY, M.J., et al., Image-guided radiosurgery for the spine and pancreas, *Comput Aided Surg* **5** 4 (2000) 278-88.
- [106] MURPHY, M., et al., The management of imaging dose during image-guided radiotherapy: Report of the AAPM Task Group 75, *Med Phys* **34** 10 (2007) 4041-4061.
- [107] JAFFRAY, D.A., DRAKE, D.G., MOREAU, M., MARTINEZ, A.A., WONG, J.W., A radiographic and tomographic imaging system integrated into a medical linear accelerator for localization of bone and soft-tissue targets, *Int J Radiat Oncol Biol Phys* **45** 3 (1999) 773-89.
- [108] JAFFRAY, D.A., SIEWERDSEN, J.H., WONG, J.W., MARTINEZ, A.A., Flat-panel cone-beam computed tomography for image-guided radiation therapy, *Int J Radiat Oncol Biol Phys* **53** 5 (2002) 1337-49.
- [109] POULIOT, J., et al., Low-dose megavoltage cone-beam CT for radiation therapy, *Int J Radiat Oncol Biol Phys* **61** 2 (2005) 552-60.
- [110] FELDKAMP, L.A., DAVIS, L.C., KRESS, J.W., Practical cone-beam algorithm, *J. Opt. Soc. Am* **1** (1984) 612-619.
- [111] SHARPE, M.B., et al., The stability of mechanical calibration for a kV cone beam computed tomography system integrated with linear accelerator, *Med Phys* **33** 1 (2006) 136-44.
- [112] FENWICK, J.D., et al., Quality assurance of a helical tomotherapy machine, *Phys Med Biol* **49** 13 (2004) 2933-53.

- [113] LEHMANN, J., PERKS, J., SEMON, S., HARSE, R., PURDY, J.A., Commissioning experience with cone-beam computed tomography for image-guided radiation therapy, *J Appl Clin Med Phys* **8** 3 (2007) 2354.
- [114] YOO, S., et al., A quality assurance program for the on-board imagers, *Med Phys* **33** 11 (2006) 4431-47.
- [115] MUTIC, S., et al., Multimodality image registration quality assurance for conformal three-dimensional treatment planning, *International Journal of Radiation Oncology Biology Physics* **51** (2001) 255.
- [116] FITZPATRICK, J.M., WEST, J.B., MAURER, C.R., JR., Predicting error in rigid-body point-based registration, *IEEE Trans Med Imaging* **17** 5 (1998) 694-702.
- [117] BROCK, K.K., SHARPE, M.B., DAWSON, L.A., KIM, S.M., JAFFRAY, D.A., Accuracy of finite element model-based multi-organ deformable image registration, *Med Phys* **32** 6 (2005) 1647-59.
- [118] KAUS, M.R., et al., Assessment of a model-based deformable image registration approach for radiation therapy planning, *Int J Radiat Oncol Biol Phys* **68** 2 (2007) 572-80.
- [119] VOS, P.H., "Decision criteria and correction strategies in the clinical use of electronic digital portal imagers." Proceedings of the XIIth International Congress of Computers in Radiotherapy., (LEAVITT, D.D., STARKSCHALL, G., Ed.), Medical Physics Publishing, Madison, (1997) 33-36.
- [120] BEL, A., et al., High-precision prostate cancer irradiation by clinical application of an offline patient setup verification procedure, using portal imaging, *Int J Radiat Oncol Biol Phys* **35** 2 (1996) 321-32.
- [121] DE BOER, H.C., HEIJMEN, B.J., A protocol for the reduction of systematic patient setup errors with minimal portal imaging workload, *Int J Radiat Oncol Biol Phys* **50** 5 (2001) 1350-65.
- [122] YAN, D., et al., Adaptive modification of treatment planning to minimize the deleterious effects of treatment setup errors, *Int J Radiat Oncol Biol Phys* **38** 1 (1997) 197-206.

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